

The Clinical Pharmacology of Lidocaine as an Antiarrhythmic Drug

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom at the end of each academic year to ask the incumbent chief medical residents to speak at Medical Grand Rounds. It offers us a chance to thank them publicly for their participation in our academic program during the year. Ken Collinsworth has entered the navy and is serving as staff cardiologist at Oak Knoll Naval Hospital. He has returned today to speak on the clinical pharmacology of lidocaine as an antiarrhythmic drug. I want to express my personal appreciation for the distinguished way in which he served as chief medical resident in the Department of Medicine during this past year.*

DR. COLLINSWORTH:† Thank you, Dr. Smith. Today, I plan to discuss the clinical pharmacology of lidocaine and some aspects of its use. First, I will briefly describe the chemistry and metabolism of lidocaine.¹ The chemical structure of lidocaine is one of an aromatic group, 2,6-xylylidine, to which is coupled diethylglycine by an amide

bond. It is metabolized chiefly by the liver, and the major pathway of degradation as illustrated in Figure 1 appears to be conversion to monoethylglycylxylylidine, to 2,6-xylylidine and finally to 4-hydroxy-2,6-xylylidine. These and various other metabolites are excreted in the urine. In addition, a small percentage of unchanged lidocaine, up to 10 percent, is also excreted in the urine. The major metabolic end product is 4-hydroxy-2,6-xylylidine since up to 70 percent of an administered dose of lidocaine appears as this compound in the urine. The cyclic form has now been recognized to be the result of laboratory artifact and is not a usual metabolite, and the N-hydroxy forms are now considered not to occur in humans.

It is useful to review the electrophysiologic effects of lidocaine as a background for understanding its antiarrhythmic actions. Applying experimental results to clinical medicine is risky and especially so with lidocaine. The electrophysiologic studies have been carried out mostly in isolated heart preparations using different parts of the myocardium from a variety of different animal species with the attendant possibility of species

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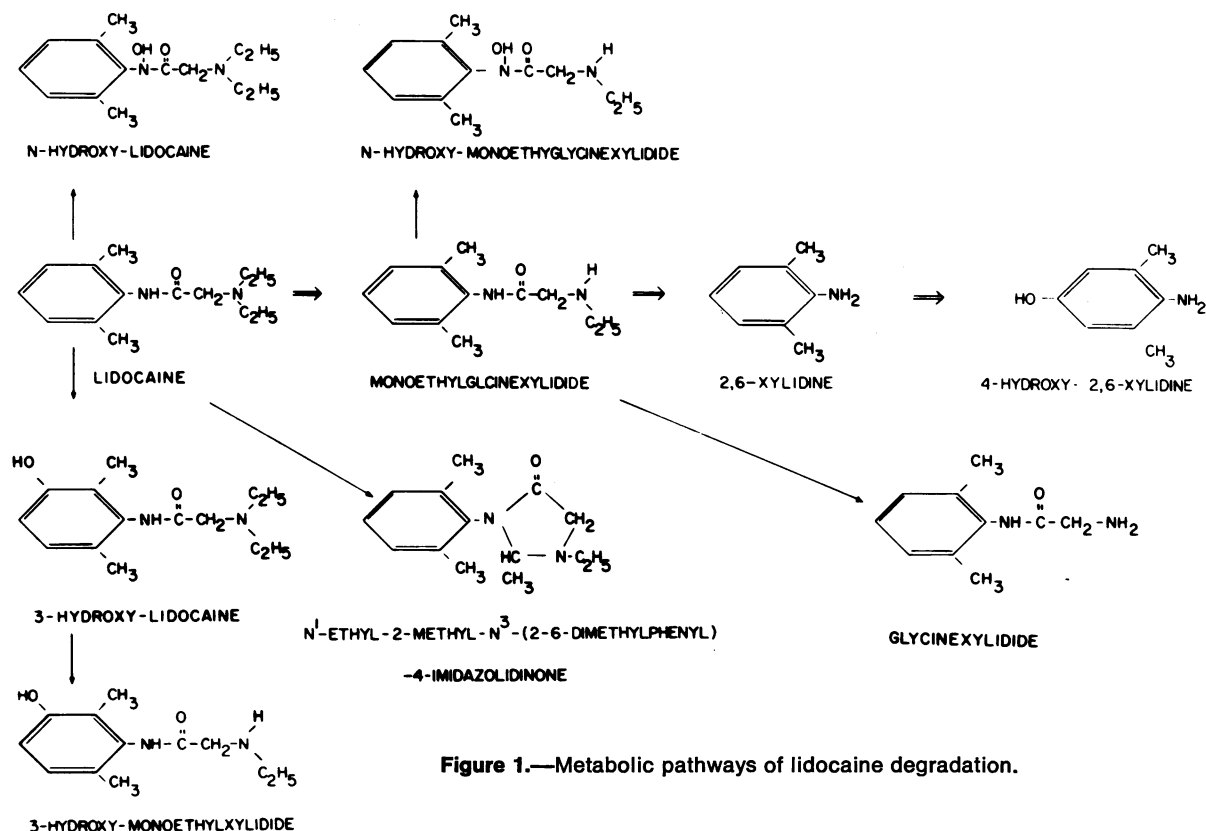


Figure 1.—Metabolic pathways of lidocaine degradation.

and tissue variation. Most of these studies have been done with presumably normal, undamaged myocardium, in well oxygenated tissue baths but without the microvasculature perfused. Various potassium concentrations have been present in the bathing media. Because of these variations in study technique many of the resulting data are conflicting. To extrapolate these data to explain why lidocaine suppresses the cardiac arrhythmias in humans in the setting of acutely ischemic or infarcted hearts possessing intact autonomic nervous systems with various degrees of activity, must be considered purely speculative. Nevertheless, a common consensus of the electrophysiologic actions of lidocaine seems to be emerging from the literature.^{1,2a,2b}

In Figure 2, an idealized monophasic action potential from a Purkinje fiber is depicted. The normal action potential is represented by the solid line, while the dashed line represents the action potential after lidocaine is present in the tissue bath at a concentration which would be equivalent to a therapeutic dose of lidocaine in humans. The rate of spontaneous depolarization (phase 4) which accounts for the automaticity of pacemaker tissue, appears to be decreased by

therapeutic levels of lidocaine. The duration of the action potential is decreased, but perhaps more important, the effective refractory period (during which time the fiber is unresponsive to stimuli) is not comparably shortened. Therefore, the Purkinje fiber is inexcitable for a greater fraction of the depolarization-repolarization cycle.

The maximal rate of depolarization of the

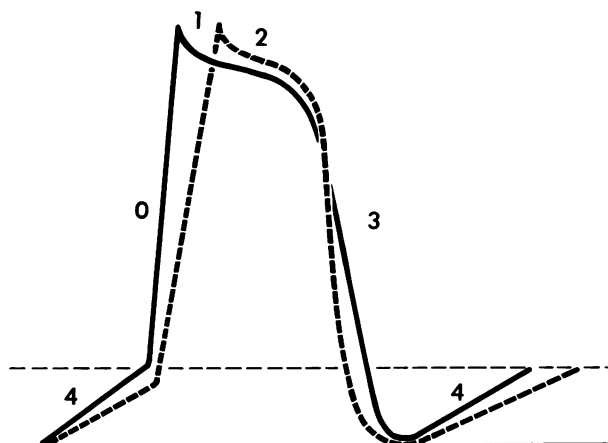


Figure 2.—Monophasic action potential of Purkinje cell. Solid line represents normal action potential. Dashed line represents action potential after lidocaine present.

action potential during the phase 0 period is controversial. Bigger's studies^{2a} have shown that the maximum rate of depolarization is accelerated by lidocaine, whereas Singh and Williams^{2b} have shown that the maximum rate of depolarization is decreased by lidocaine. The conflicting results probably are due to the different potassium concentrations used in the tissue baths since potassium can influence the transmembrane potential and thus the rate of depolarization. I personally believe that the evidence is in favor of lidocaine slowing phase 0; however, this effect appears to be much less than that induced by procainamide or quinidine. The conduction velocity in Purkinje fibers appears to be decreased slightly, consistent with a decreased maximal rate of depolarization. It has also been shown that the fibrillation threshold is increased by lidocaine, that is, more current must be applied to induce the tissue to fibrillate during the vulnerable period of the cardiac cycle. At therapeutic concentrations of lidocaine, the Purkinje system appears electrophysiologically to be most affected, with lesser effect produced on the ventricular muscle and still less effect on the sinus and atrioventricular (AV) nodes and atrial muscle.

The two major theories of the cause of ventricular arrhythmias are: (1) enhanced automaticity by Purkinje pacemaker tissues in the ventricle and (2) reentry due to slowed or decremental conduction through ischemic or damaged myocardium. As to arrhythmias caused by increased automaticity of pacemaker tissue in the ventricle, lidocaine may well have its antiarrhythmic effect by suppressing the phase 4 spontaneous depolarization and, therefore, suppressing the automaticity. The reentrant arrhythmias, on the other hand, may be suppressed by lidocaine's effect on altering conduction velocity and action potential, in this way interfering with the reentrant pathway.

We can now discuss the antiarrhythmic uses of lidocaine. Lidocaine has been shown to abolish or to decrease ventricular premature beats and to terminate ventricular tachycardia occurring in a variety of clinical situations. It has been shown to be effective during general surgical procedures, during cardiac surgical operation, after acute myocardial infarction and in the presence of stable ventricular premature beats occurring in a variety of cardiac diseases—including coronary artery disease and cardiomyopathies. It has been effectively used in the presence of digitalis intoxi-

cation. In patients with acute myocardial infarctions in a coronary care unit, it has been shown that in approximately 80 percent ventricular premature beats will be abolished or decreased by lidocaine.³

Several controversies remain concerning the use of lidocaine in acute infarction, however. Several reports indicate that in the first one or two hours following the appearance of the symptoms of infarction, administration of lidocaine is much less effective treatment for ventricular premature beats than it is after several hours following the onset of symptoms. One article reported a series of patients with acute myocardial infarction treated with lidocaine within four hours of the onset of symptoms.⁴ In 30 percent of patients ventricular premature beats were abolished, in 19 percent they were decreased and in 20 percent there was no effect. It is interesting that in 19 percent there actually was an increase in the number of ventricular premature beats shortly after lidocaine was administered and occasionally even ventricular tachycardia developed. There are animal studies which also show enhancement of ventricular premature beats following lidocaine administration in the early stages of experimental infarction. The usefulness of antiarrhythmic agents in the earlier stages of infarction is important since approximately two thirds of the deaths from acute myocardial infarction which are believed to be due mostly to ventricular fibrillation occur during the first hour after the onset of symptoms.⁵

The cause for apparent insensitivity to lidocaine during early acute infarction is not known. Some investigators feel that the mechanism producing arrhythmias during early acute infarction differs from that occurring later in the course of infarction.⁶ Adrenalin and sympathetic nervous system activity may be notably increased in early acute infarction causing the ventricular premature beats. There is a small clinical experience in patients with infarctions to suggest that practolol, a beta adrenergic blocking agent, is effective in treating the acute phase ventricular premature beats but not the later stage ventricular premature beats. There is also some evidence from experimental infarctions in animals to suggest that adrenalin may play an important role in the genesis of ventricular premature beats that are responsive to beta adrenergic blockers but not to lidocaine. One study recently reviewed the results of administering lidocaine intramuscularly to one large group

of patients in doses known to produce therapeutic blood levels, and a placebo to a second large group of patients when first seen in the prehospital phase for symptoms suggesting acute infarction.⁷ Of those who ultimately were shown to have had infarctions, the lidocaine treated group had a slightly, but significantly, lower incidence of early mortality. The late mortalities were not different in the treated and the untreated groups after entering the coronary care unit and were usually due to pump failure.

Another controversy exists as to whether prophylactic lidocaine should be given to prevent ventricular fibrillation in all patients with acute infarction as they enter the coronary care unit. The rationale has been that ventricular fibrillation in acute infarction is usually preceded by a premonitory ventricular arrhythmia. The usual indications for administering lidocaine to patients with acute infarction are the following: (1) when more than five ventricular premature beats of unifocal origin occur per minute; (2) when the R waves of premature ventricular beats are noted on the T waves of the previous contraction; (3) when multifocal ventricular premature beats occur; (4) when two or more ventricular premature beats occur in sequence, that is to say short bursts of ventricular tachycardia, and (5) during sustained ventricular tachycardia. The feeling has been that primary ventricular fibrillation is likely to follow the types of ventricular arrhythmias just mentioned and suppression of such arrhythmias is indicated. Primary ventricular fibrillation is defined as ventricular fibrillation occurring in the absence of cardiogenic shock or severe congestive heart failure. Several studies have approached this problem and the results are not conclusive. Either a small or no decrease in primary ventricular fibrillation is found when comparing prophylactically lidocaine-treated *versus* placebo-treated groups of patients with acute infarction in a coronary care unit.^{8,9} It is of interest that in these studies, which show either some or no decrease in primary ventricular fibrillation, the ultimate mortalities of the treated and the untreated groups with infarction were essentially the same after they entered the coronary care unit, and death was usually due to pump failure or cardiac rupture and not arrhythmias.

My conclusions are the following: (1) prophylactic lidocaine probably should not be given to every patient with suspected or proven acute infarction in the coronary care unit; (2) so-called

premonitory arrhythmias should be treated; (3) primary ventricular fibrillation is not a major cause of mortality in the coronary care unit and can be effectively treated by electrical conversion; (4) pump failure and cardiac rupture are the major causes of death in the coronary care unit. The conclusions that I have drawn from the studies about lidocaine in patients with acute infarction before their admission to hospital are that if ventricular arrhythmias are present in a patient with suspected acute infarction when first seen at home or generally before entering the hospital, he or she should be given intramuscular lidocaine. Lidocaine in a dosage of 300 mg administered into the deltoid muscle will provide therapeutic blood levels. In the absence of ventricular arrhythmias or in the presence of bradycardia or hypotension, lidocaine should not be given without adequate monitoring. The reasons are that ventricular fibrillation in a coronary care unit can be treated effectively with electrical conversion but such treatment may not be possible in the prehospital phase, and lidocaine may just provide the necessary antiarrhythmic protection even though its efficacy may be less in the first two hours after infarction.

Lidocaine has not been effective in certain cardiac arrhythmias: (1) it has not been very effective in terminating ventricular fibrillation after it has already begun; (2) it has generally not been effective in terminating supraventricular arrhythmias. It might be reasoned that this would be the case since experimentally the action potential in atrial muscle, sinus nodal or AV nodal tissue is, as mentioned above, little altered by lidocaine.

It has been found that blood levels above 1.2 micrograms (μg) per ml are therapeutic, the therapeutic range being defined as between 1.2 and 5.0 μg per ml over which range there was in 80 percent of patients with ventricular premature beats suppression or a significant decrease in ventricular ectopy.³ A dose response relationship was defined, such that for any given patient, ventricular premature beats were progressively suppressed as the blood level increased. The toxic range has been defined as being greater than 5 μg per ml. In the 5 to 9 μg per ml range, toxicity will be seen in a few patients. Above 9 μg per ml at least some manifestations of toxicity will be seen in most patients.

I will now turn to a discussion of the pharmacokinetics of lidocaine. First, the blood level of lidocaine following an intravenous bolus can be

depicted by a biphasic curve, as shown in Figure 3. Initially the blood level falls rapidly with a half-life of approximately ten minutes. This is mainly due to drug mixing and distribution to the peripheral tissues. A second, delayed fall then appears with a half-life of about two hours and follows first order kinetics. This is mainly due to clearance by the liver. Because mixing and distribution occur rapidly during constant intravenous infusion, the value of a slower half-life of about two hours should be used in determining dosages and blood levels. Using the half-life value of two hours, a constant infusion then takes about six hours to attain 90 percent of the steady state levels and up to about ten hours before steady state levels are actually reached. After discontinuing an infusion at steady state levels, the half-life of blood level is the same as the slower second curve, that is, about two hours.

In treating arrhythmias, understanding the pharmacokinetics of lidocaine is important. First,

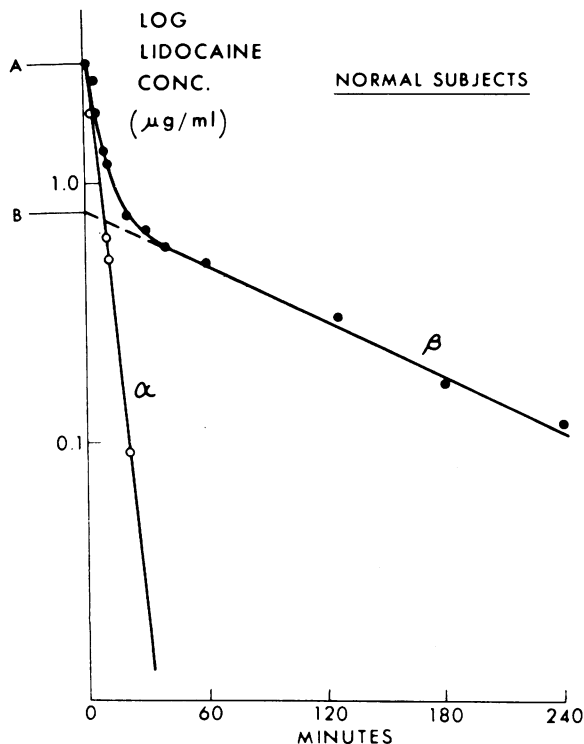


Figure 3.—A biphasic curve following a single intravenous bolus of 50 mg of lidocaine. A and B are the zero time intercepts of data plotted on semilogarithmic paper, while α and β are the rapid and slow time constants, respectively. The closed circles represent observed data, whereas open circles represent derived data. (Reprinted with permission of Thomson PD, et al and Am Heart J: The influence of heart failure, liver disease, and renal failure on the disposition of lidocaine in man. Am Heart J 82:417, 1971)

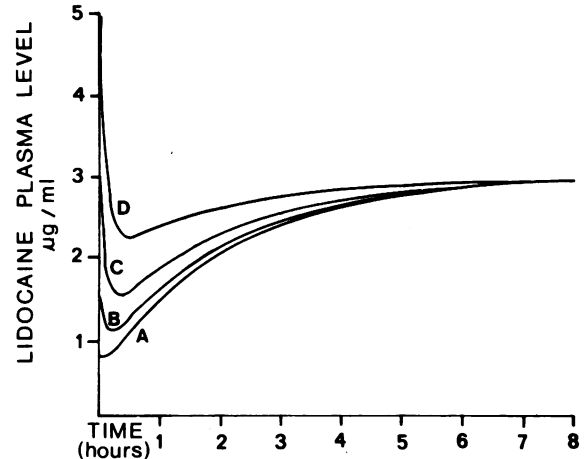


Figure 4.—Calculated lidocaine plasma level curves where a 4 mg per minute infusion has been combined with a 40 (A), 80 (B), 160 (C) and 320 (D) mg rapid intravenous dose. (Reprinted with permission of Boyes and Keenaghan¹⁹).

an intravenous bolus will rapidly provide blood levels in the therapeutic range and suppress arrhythmias, but since the blood levels fall very rapidly, arrhythmias often return within 15 to 20 minutes. Therefore, intravenous bolus administration alone is not a practical way to treat a persistent arrhythmia. On the other hand, a constant infusion alone may take two or three hours at a minimum before therapeutic levels are achieved and the arrhythmia suppressed. Constant infusion alone then is not a practical way to treat a serious acute arrhythmia. Both intravenous bolus and constant infusion are combined in order to provide therapeutic blood levels at all times after beginning therapy. Figure 4 shows the resultant blood level curves of different initial bolus doses but with the same constant infusion rate. A minimum level is reached at about 30 minutes followed by a slow rise to steady state levels. At the lowest point the blood level may drop below the therapeutic range and arrhythmias may break through. If this occurs, a small bolus dose of perhaps a quarter to a half of the initial bolus can be given slowly to increase the blood level until the constant infusion raises the blood level above the minimum therapeutic level.

It is important to choose the correct dosage, both for the intravenous bolus and the constant infusion rate, to achieve adequate therapeutic blood levels without pushing them into the toxic range. To do this requires an understanding of the pharmacokinetics of lidocaine. Clearance of lidocaine is mainly by hepatic metabolism which is very rapid, such that the actual rate of clearance de-

TABLE 1.—*Dosage Recommendations*

<i>Normal cardiac output and liver function</i>
150 mg bolus, 4 mg per minute infusion
<i>Mild-moderate decreased cardiac output or liver disease</i>
100 mg bolus, 2-3 mg per minute infusion
<i>Notably decreased cardiac output or shock</i>
50 mg bolus, 1 mg per minute or less infusion

depends upon hepatic blood flow. In patients with reduced cardiac output and congestive heart failure, whether it is acute or chronic, the hepatic blood flow, which is proportional to cardiac output, and the drug clearance are decreased such that any given rate of lidocaine infusion will result in higher blood levels. In patients with liver failure, hepatic clearance may also be reduced though there tends to be much variability in the degree of reduction. In addition, in patients with congestive heart failure there is decreased volume of distribution of lidocaine presumably because of diminished perfusion to the peripheral tissues. This also leads to increased blood levels at any given infusion rate. These concepts of pharmacokinetics are well covered in recent articles.^{10,11}

Using this information and clinical experience, dosage recommendations for lidocaine administration can be made.¹ The dosages given in Table 1 are for a man weighing 70 kilograms and it must be realized that a weight adjustment must be made since the volume of distribution also depends on the size of the patient. These dosages have been worked out to provide effective therapeutic levels at all times after the initiation of bolus. In patients with normal cardiac output and liver function, a 150 mg bolus followed by a 4 mg per minute infusion will provide therapeutic levels. It is probably not likely that lidocaine will be administered at dosages this high because most patients requiring lidocaine do have cardiac disease and many of them will have diminished cardiac output. The next dosage recommendation range is for those with a mildly to moderately decreased cardiac output, or those with liver disease. A 100 mg bolus followed by a 2 to 3 mg per minute infusion will provide therapeutic blood levels. Whether it be a 2 or 3 mg per minute infusion would depend upon clinical judgment as to the patient's cardiac output. Finally, in patients with notably decreased cardiac output, or those who are in shock, no more than a 50 mg bolus followed by a 1 mg per minute infusion is recommended; and in certain instances these dosages may well be excessive. In patients who are in

shock, for example, liver blood flow and clearance of lidocaine may be severely reduced, such that even small dosages may rapidly lead to toxic blood levels. Intramuscular injection will also provide therapeutic blood levels that are effective in treating arrhythmias. A dosage of 300 mg of lidocaine administered as a 10 percent solution in the deltoid muscle will provide therapeutic blood levels in about 10 to 15 minutes persisting for at least an hour. Intramuscularly given lidocaine may have a place in treating arrhythmias in patients with acute infarctions seen before they get to the hospital. Orally administered lidocaine does not provide effective blood levels because it is mostly removed from the portal blood by the liver before it reaches the systemic circulation.

When giving lidocaine, administer the intravenous bolus slowly, at least over one or two minutes. Too rapid an administration is probably the most common cause for lidocaine toxicity. An immediate injection leads to extremely high blood levels since at least a few minutes are needed for dilution and distribution of the drug. Commonly, however, lidocaine is rapidly administered as an all-at-once bolus, and it is not surprising that patients complain of dizziness or other toxic symptoms following such rapid injection. With regard to constant infusion, it is certainly possible to attain therapeutic blood levels quite rapidly using a higher than usual rate of infusion, such as 6 to 8 mg per minute, but the ultimate steady state levels are certainly going to be in the toxic range since the clearance rate of the drug will not change and the higher the infusion rate the higher the resultant steady state level. A patient with moderately severe congestive heart failure may do well for the first several hours on a 4 mg per minute infusion and arrhythmias may be controlled, but sometime later in the day the blood levels very likely will be in the toxic range. Understanding the half-life principle is important for adjusting an ongoing, constant infusion rate. If arrhythmias develop while constant infusion is being carried out, and a higher blood level is desired to see whether that will control the arrhythmia, turning up the infusion rate from 2 to 3 mg per minute will require perhaps an hour before the blood level has substantially increased. In this situation small bolus doses of 10 to 25 mg may be given slowly and repeated every 20 to 30 minutes, or at briefer intervals. This should increase the blood level substantially without resulting in toxic levels. If blood levels during constant in-

fusion are recognized as being toxic, it must be understood that after stopping the infusion the toxic symptoms may persist for some time, since approximately two hours will pass before the blood level decreases to 50 percent of the blood level at the termination of the infusion. If lidocaine blood level assay is rapidly available, such a determination may be helpful for adjusting the rate of infusion.

I now will discuss some aspects of the side effects and toxicity of lidocaine. Central nervous system (CNS) toxicity is the most common side effect of lidocaine and is the result of excessive blood levels, as mentioned earlier. Blood levels from 5 to 9 μg per ml are associated with occasional side effects and blood levels greater than 9 μg per ml are commonly associated with CNS side effects. The milder signs of CNS toxicity include dizziness, drowsiness, paresthesias, disorientation, agitation, twitching, double vision and diminished hearing. Severe side effects include seizures and respiratory arrest. Almost all instances of CNS toxicity represent clear-cut overdoses. Immediately after an intravenous bolus given too quickly, very high blood levels appear and since brain and blood lidocaine levels equilibrate quickly, very high brain levels result and lead to toxic effects. Fortunately, after an intravenous bolus the blood and thus brain levels decrease within minutes and symptoms of CNS toxicity diminish rapidly. This sequence is probably the most common example of lidocaine toxicity. If CNS toxicity occurs during constant infusion, the blood and the CNS symptoms take longer to decrease. Seizures do respond well to small doses of intravenous diazepam. The contribution of the metabolic products of lidocaine degradation to toxic effects is not clear at this time. Two of the major metabolites, monoethylglycylxylidide and glycylxylidide, may, however, be responsible for CNS toxicity in some cases, and some documentation exists for this in humans during constant infusion.¹² In animals monoethylglycylxylidide can clearly induce convulsive activity equivalent to that of lidocaine. Also, in animals the convulsive effects of lidocaine are added to that of its metabolites.

I would now like to review the cardiac side effects. When delivered in a way that results in therapeutic blood levels,¹ lidocaine appears to cause no or minimal decrease in cardiac pump function as measured by ventricular contractility, cardiac output, arterial pressure or heart rates in

normal humans, in patients with chronic cardiac disease and in patients with acute infarction. Overdosage, however, can clearly cause hypotension, likely due to a direct depressant effect on the myocardial contractility, especially in a damaged heart. This again usually occurs when an intravenous bolus is injected much too rapidly resulting in high blood levels but, fortunately, usually is also transient. In pacemaker tissue, subsidiary pacemaker tissues (such as those in the Purkinje system) seem to be suppressed more than sinus or junctional tissues. Findings in most human and animal studies support this statement and show minimal changes in the sinus or junctional rates after administering therapeutic doses of lidocaine. This generalization would appear to apply to patients with normal hearts, patients with chronic heart disease and patients with acute infarctions. This generalization would also include those patients with acute infarction with sinus bradycardia.¹³ However, there are numerous published case reports and many anecdotes about sinus bradycardia, sinus arrest or junctional rhythm depression developing in patients after intravenous administration of lidocaine. Most of these instances again appear to be due to overdoses, are usually transient and are usually associated with CNS toxicity following too rapidly administered lidocaine. Yet, there are a few reports, usually in the setting of the sick sinus syndrome and in acute infarction, in which sinus slowing or arrest has resulted from apparently appropriately administered doses of lidocaine. Thus, caution must clearly be used when sinus dysfunction, atrioventricular block or junctional rhythm is present. However, in most cases, lidocaine administration may be safely used.

Results of His's bundle studies have shown that lidocaine may be safely used in patients with chronic intraventricular conducting defects (such as right bundle-branch block, left bundle-branch block or with atrioventricular nodal delay) without increasing the block at lidocaine blood levels which are considered therapeutic and were effective in abolishing arrhythmias.¹⁴ Again, these were patients with chronic conduction defects, not patients with recent infarction or congestive heart failure. There are isolated reports in the literature citing examples of various degrees of increased heart block following lidocaine administration, mostly in patients with acute infarction. Again, in most of these reports lidocaine bolus overdosage appears to have been the cause of the

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heart block. However, there remain a few instances of heart block that have been shown to follow apparently appropriate doses of lidocaine. The message, then, is the same as that concerning pacemaker tissue suppression. Lidocaine in appropriate doses is generally safe in treating patients with conduction disturbances, but caution must be used particularly with the rate of bolus administration.

To conclude, I will comment on allergic reactions. We always ask our patients about local anesthetic reactions before administering lidocaine and consider cross-reactions. However, the actual documentation of true allergic reactions to lidocaine (whether anaphylactic reactions, skin rashes or angioedema) is extremely rare in the literature, but there are a few well documented reports on the subject. In addition, patients with allergic reactions to other local "caine" anesthetics probably do not manifest cross allergy to lidocaine; this appears to be true at least for procaine hydrochloride (Novocain®).

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